MICRONEEDLE COMPOSITIONS AND METHODS OF USING SAME

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 15/403,989, filed Jan. 11, 2017, now issued and U.S. patent Ser. No. 10/022,436 on Jul. 17, 2018, which claims the benefit of U.S. Provisional Application No. 62/277,312, filed on Jan. 11, 2016, both of which are incorporated herein by reference in their entireties.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Jan. 31, 2017, is named 47750701301 SL.txt and is 552 bytes in size.

BACKGROUND OF THE INVENTION

Delivery of compositions to a target cell or tissue faces various transport barriers. Nucleic acids that encode gene products, such as proteins, and non-coding RNA (e.g., siRNAs) can be delivered directly to a desired vertebrate subject, or can be delivered ex vivo to cells obtained or derived from the subject, and the cells can be re-implanted into the subject. Delivery of such nucleic acids to a vertebrate subject is desirable for many purposes, such as, for gene therapy, to induce an immune response against an encoded polypeptide, or to regulate the expression of endogenous genes. The use of this approach has been hindered because free DNA is not readily taken up by cells and free RNA is rapidly degraded in vivo. Moreover, delivery can also be problematic. For instance, subcutaneous or intramuscular injections using hypodermic needles can cause pain, trauma, and anxiety in a subject.

Delivery of one or more polypeptides, whether directly as protein or indirectly by an encoding polynucleotide, has many useful applications, including vaccination. Vaccination has proven an effective means to fight and even eradicate infectious diseases. The influenza vaccine, for example, is currently recommended by the CDC as the primary method for preventing influenza. However, influenza virus has a high rate of mutation and antigenic variation and a new vaccine is typically produced each year based upon the predicted circulating pathogenic strains. This poses a number of challenges. For instance, the effectiveness of the vaccine is only as good as the prediction. If the prediction of the dominant strain is incorrect, the vaccine will have limited effectiveness for most people. Further, it can take months to produce enough influenza vaccine to vaccinate a population.

SUMMARY OF THE INVENTION

Disclosed herein, in some embodiments, are microneedle devices for administering an RNA molecule, comprising: (a) a substrate comprising a plurality of microneedles; and (b) a composition comprising an RNA encoding an exogenous polypeptide coated onto or embedded into the plurality of microneedles. In some embodiments, the RNA molecule is a recombinant alphavirus replicon. In some embodiments, the RNA molecule is dehydrated. In some embodiments, the plurality of microneedles are dissolvable, biosoluble, or

biodegradable. In some embodiments, the exogenous polypeptide is a foreign or a self-antigen. In some embodiments, the self-antigen is an antigen associated with a cancer. In some embodiments, the foreign antigen is an antigen associated with an infectious agent. In some embodiments, the recombinant alphavirus replicon is present in an amount effective to induce an immune response to the foreign or self-antigen. In some embodiments, the exogenous polypeptide is an influenza virus HA or NA polypeptide. In some embodiments, the influenza virus HA polypeptide is an influenza A virus HA polypeptide or an influenza B virus HA polypeptide. In some embodiments, the influenza virus HA polypeptide is from a viral strain of a group 1 influenza A virus subtype selected from H1, H2, H5, H6, H8, H9, H11, H12, H13, H16, H17, or H18. In some embodiments, the influenza virus HA polypeptide is from a viral strain of a group 2 influenza A virus subtype selected from H3, H4, H7, H10, H14, or H15. In some embodiments, the influenza virus HA polypeptide is from a viral strain of an influenza B virus. In some embodiments, the influenza virus HA polypeptide is from a viral strain of an influenza A virus H1 subtype. In some embodiments, the influenza virus HA polypeptide is from a viral strain of an influenza A virus H3 subtype. In some embodiments, the influenza virus HA polypeptide is from a viral strain of an influenza B virus Yamagata or Victoria lineage. In some embodiments, the recombinant alphavirus replicon encodes an exogenous polypeptide comprising: (a) an HA polypeptide from a viral strain of an influenza A virus H1 subtype; (b) an HA polypeptide from a viral strain of an influenza A virus H3 subtype; (c) an HA polypeptide from a viral strain of an influenza B virus Yamagata lineage; (d) an HA polypeptide from a viral strain of an influenza B virus Victoria lineage; or (e) any combinations thereof. In some embodiments, the recombinant alphavirus replicon encodes at least two exogenous polypeptides comprising: (a) an HA polypeptide from a viral strain of an influenza A virus H1 subtype; (b) an HA polypeptide from a viral strain of an influenza A virus H3 subtype; (c) an HA polypeptide from a viral strain of an influenza B virus Yamagata lineage; or (d) an HA polypeptide from a viral strain of an influenza B virus Victoria lineage. In some embodiments, each of the exogenous polypeptides are encoded on a single recombinant alphavirus replicon. In some embodiments, the exogenous polypeptides are encoded on different recombinant alphavirus replicons. In some embodiments, the exogenous polypeptide is a hepatitis B virus surface antigen (HBsAg). In some embodiments, the recombinant alphavirus replicon encodes an exogenous polypeptide comprising: (a) an antigen from a polio virus; (b) an antigen from *Clostridium tetani*; (c) an antigen from a rabies virus; or (d) any combinations thereof. In some embodiments, the recombinant alphavirus replicon encodes an exogenous polypeptide comprising: (a) an antigen from a polio virus; (b) an antigen from *Clostridium tetani*; and (c) an antigen from a rabies virus. In some embodiments, each of the exogenous polypeptides are encoded on a single recombinant alphavirus replicon. In some embodiments, the exogenous polypeptides are encoded on different recombinant alphavirus replicons. In some embodiments, the recombinant alphavirus replicon encodes an exogenous polypeptide comprising: (a) an antigen from a Marburg virus; (b) an antigen from an Ebola Sudan virus; (c) an antigen from an Ebola Zaire virus; or (d) any combinations thereof. In some embodiments, the recombinant alphavirus replicon encodes an exogenous polypeptide comprising: (a) an antigen from a Marburg virus; (b) an antigen from an Ebola Sudan virus; and (c) an antigen from